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Trends in the use of pre-operative radiation for adenocarcinoma of the pancreas in the United States

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Abstract

Background: The benefit and timing of radiation therapy (RT) for patients undergoing a resection for pancreatic adenocarcinoma remains unclear. This study identifies trends in the use of radiation over a 10-year period and factors associated with the use of pre-operative radiation, in particular.

Methods: The Surveillance, Epidemiology and End Results registry was used to identify patients aged ≥18 years with pancreatic adenocarcinoma who underwent a surgical resection between 2000 and 2010. Logistic regression was used to identify time trends and factors associated with the use of pre-operative radiation.

Results: The overall use of radiation decreased with time among the 8474 patients who met the inclusion criteria. However, the use of pre-operative radiation increased from 1.8% to 3.9% ($P \leq 0.05$). Factors significantly associated with receipt of pre-operative radiation were younger age, treatment in more recent years and having an advanced T-stage tumour. The 5-year hazard of death was significantly less for those who received pre-operative radiation versus surgery alone [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.55–0.74] and for those who received post-operative radiation versus surgery alone (HR 0.69, 95% CI 0.65–0.73).

Discussion: The use of pre-operative radiation significantly increased during the study period. However, the overall use of pre-operative radiation therapy remains low in spite of the potential benefits.

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Introduction

A number of studies have investigated the outcomes associated with the use of post-operative adjuvant radiation therapy (RT) for the treatment of pancreatic adenocarcinoma. The findings of these studies have been largely inconsistent with some showing a significant survival benefit with the use of chemoradiation[1–4] and others showing only a non-significant trend towards an increase in survival.[5–7] Complicating the picture further, the European Study Group for Pancreatic Cancer Trial 1 (ESPAC-1) results suggested that post-operative chemoradiation may even have a deleterious effect on survival.[8] This uncertainty regarding the benefits of post-operative chemoradiation is reflected in the National Comprehensive Cancer Network (NCCN) guidelines for post-operative adjuvant treatment of pancreatic adenocarcinoma. After surgical resection, the NCCN guidelines recommend enrolment in a clinical trial of post-operative adjuvant therapy. If a clinical trial is not an option, the NCCN guidelines recommend either chemoradiation or chemotherapy alone as appropriate post-operative adjuvant therapy.[9]

While the utility of post-operative radiation has been questioned, several single-institutional studies have reported the outcomes and potential benefits of pre-operative chemoradiation.[10–14] Current NCCN guidelines recommend pre-operative adjuvant therapy as an appropriate option for those with borderline resectable disease and acknowledge that many NCCN member institutions now prefer this approach for

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borderline resectable patients. For patients with resectable disease, the panel recommends these patients enrol in a clinical trial when pursuing pre-operative adjuvant therapy as opposed to a surgery first approach.[9] Currently, there are few data on the frequency and trends of the use of pre-operative RT in the United States or the predictive factors related to receipt of pre-operative radiation therapy. This study evaluated trends in the use of radiation in the pre- and post-operative setting, and sought to identify demographic, patient and tumour predictors that play a role in clinical decision-making. In addition, potential differences in survival were assessed between those patients who received RT (either pre- or post-operative) versus those who underwent surgery alone.

Methodology

Data

The Surveillance Epidemiology and End Results (SEER) programme database was used to examine trends in the use of pre- and post-operative RT for patients who underwent a resection for the treatment of pancreatic adenocarcinoma between 2000 and 2010. The SEER cancer registries provide population-based cancer surveillance for 18 areas that represent approximately 28% of the United States.[15] SEER collects patient demographic and tumour characteristics, including age at diagnosis, race, primary tumour site, tumour laterality, histology type, tumour stage, tumour grade, diagnostic confirmation, type of surgery, the use of radiation therapy, vital status and the cause of death.

Patients

The study was limited to include only patients aged 18 years and older diagnosed with microscopically confirmed pancreatic adenocarcinoma and who had undergone a surgical resection between 2000 and 2010. The analysis excluded patients with non-adenocarcinoma pancreatic cancer, those with multiple primary malignancies in a lifetime and those patients diagnosed while in a nursing home, by autopsy, or on a death certificate. Owing to the concern that registries with very few patients receiving pre-operative RT could skew the analysis, registries were excluded that reported fewer than 10 patients treated with pre-operative RT over the 10-year analytic period. Twelve registries were included, and the six excluded registries comprised Hawaii, New Mexico, Rural Georgia, San Francisco – Oakland, San Jose – Monterey and the Alaska Native Tumor Registry.

Three treatment categories were created: surgery without radiation, pre-operative radiation then surgery and surgery followed by post-operative radiation. Surgical codes included a partial pancreatectomy, NOS (SEER surgical code 30), local or partial pancreatectomy and duodenectomy (without distal/partial gastrectomy and with partial gastrectomy (Whipple); 35–37), a total pancreatectomy (40), a total pancreatectomy with subtotal gastrectomy/duodenectomy (60), an extended pancreatoduodenectomy (70) and a pancreatectomy, NOS (80).

Statistical analysis

Unadjusted treatment patterns were compared over the 10-year study period using the Cochrane–Armitage test for trend. Logistic regression was used to identify time trends, demographics and patient factors associated with the use of pre-operative radiation therapy. All regression models included the patients' age, race, gender, year of diagnosis, tumour size, T-stage, tumour grade, the number of lymph nodes examined, lymph node status, treatment type and registry.

The Kaplan–Meier method and Cox's proportional hazards models were employed to determine the 5-year relative hazard of death based on the treatment received. This model included the patients' age, race, gender, year of diagnosis, tumour size, T-stage, tumour grade, number of lymph nodes examined, lymph node status, treatment type and registry.

All statistical analysis was completed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA). This study was exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board because it used a de-identified data source.

Results

Description of the population

From 2000 to 2010, 8474 patients were identified who underwent a resection for pancreatic adenocarcinoma. Demographic, pathological and treatment details are provided in Table 1.

Changes in treatment patterns over time

Overall, the use of RT for pancreatic adenocarcinoma significantly decreased in the United States from 2000 to 2010 (45.9% to 32.6%, $P \leq 0.05$). However, the use of pre-operative RT modestly but significantly increased from 1.8% to 3.9% ($P \leq 0.05$). The use of surgery without radiation increased significantly ($P \leq 0.05$) from 54.1% (2000) to 67.4% (2010). At the same time, the use of post-operative radiation significantly decreased over time from 44.1% in 2000 to 28.7% in 2010 ($P \leq 0.05$). Thus, the overall decrease in the use of RT is largely due to a decrease in the use of post-operative RT (Fig. 1).

Factors associated with pre-operative RT

Younger patient age and diagnosis and treatment in more recent years were significantly associated with receipt of pre-operative radiation (Table 2). Significant geographical differences in the use of pre-operative radiation were observed but without obvious broad geographical patterns. Tumour factors that were significantly associated with an increase in pre-operative RT were missing or unknown tumour grade and advanced T stage (Table 2). Finally, there was a significant association between receiving pre-operative RT and positive lymph node status at the time of surgery (Table 2) suggesting that patients with higher stage cancers identified clinically are more likely to get pre-operative therapy. The number of lymph nodes evaluated was not significantly associated with the use of pre-operative radiation.

Table 1 Patient characteristics by treatment group

	No RT (*N* = 5039) *N* (%)	Pre-operative RT (*N* = 299) *N* (%)	Post-operative RT (*N* = 3136) *N* (%)
Year			
2000–2004	1751 (34.7)	91 (30.4)	1364 (43.5)
2005–2010	3288 (65.3)	208 (79.6)	1772 (56.5)
Age			
18–39	112 (2.2)	2 (0.6)	48 (1.5)
40–64	1939 (38.5)	179 (59.9)	1672 (53.3)
65+	2988 (59.3)	118 (39.5)	1416 (45.2)
Gender			
Male	2418 (48.0)	156 (52.2)	1606 (51.2)
Female	2621 (52.0)	143 (47.8)	1530 (48.8)
Race			
Non-Hispanic white	4214 (83.6)	249 (83.3)	2680 (85.5)
Black	549 (10.9)	38 (12.7)	342 (10.9)
Other or unknown	276 (5.5)	12 (4.0)	114 (3.6)
Tumour size			
<2 cm	604 (12.0)	21 (7.0)	298 (9.5)
≥2 cm	4210 (83.5)	259 (86.6)	2701 (86.1)
Missing	225 (4.5)	19 (6.4)	137 (4.4)
Tumour grade			
1 or 2	2860 (56.8)	141 (47.2)	1834 (58.5)
3	1594 (31.6)	81 (27.1)	1039 (33.1)
4	66 (1.3)	3 (1.0)	36 (1.1)
Missing/unknown	519 (10.3)	74 (24.7)	227 (7.2)
T-stage			
1 and 2	1440 (28.6)	52 (17.4)	653 (20.8)
3	3411 (67.7)	188 (62.9)	2314 (73.8)
4	188 (3.7)	59 (19.7)	169 (5.4)
Surgery type			
Whipple	3525 (70.0)	225 (75.3)	2325 (74.1)
Total pancreatectomy	589 (11.7)	39 (13.0)	327 (10.4)
Other	925 (18.4)	35 (11.7)	484 (15.4)
Node positive			
No	2295 (45.5)	197 (65.9)	1081 (34.5)
Yes	2744 (54.5)	102 (34.1)	2055 (65.5)
Nodes examined			
0	236 (4.7)	26 (8.7)	94 (3.0)
1–9	1930 (38.3)	120 (40.1)	1105 (35.2)
10–14	1103 (21.9)	78 (26.1)	764 (24.4)
15+	1673 (33.2)	68 (22.7)	1109 (35.4)
Unknown	97 (1.9)	7 (2.3)	64 (2.0)

Table 1 Continued

	No RT (*N* = 5039) *N* (%)	Pre-operative RT (*N* = 299) *N* (%)	Post-operative RT (*N* = 3136) *N* (%)
Registry			
Connecticut	307 (6.1)	22 (7.4)	180 (5.7)
Metropolitan Detroit	265 (5.3)	55 (18.4)	314 (10.0)
Iowa	177 (3.5)	20 (6.7)	162 (5.2)
Seattle (Puget Sound)	224 (4.4)	11 (3.7)	215 (6.9)
Utah	157 (3.1)	17 (5.7)	71 (2.3)
Metropolitan Atlanta	188 (3.7)	11 (3.7)	119 (3.8)
Los Angeles	662 (13.1)	16 (5.4)	215 (6.9)
Greater California	1228 (24.4)	44 (14.7)	630 (20.1)
Kentucky	312 (6.2)	14 (4.7)	220 (7.0)
Louisiana	287 (5.7)	27 (9.0)	217 (6.9)
New Jersey	806 (16.0)	42 (14.0)	557 (17.8)
Greater Georgia	426 (8.5)	20 (6.7)	236 (7.5)

Characteristics of patients undergoing surgery without radiation therapy (RT), pre-operative RT and post-operative RT 2000–2010 (*N* = 8474).

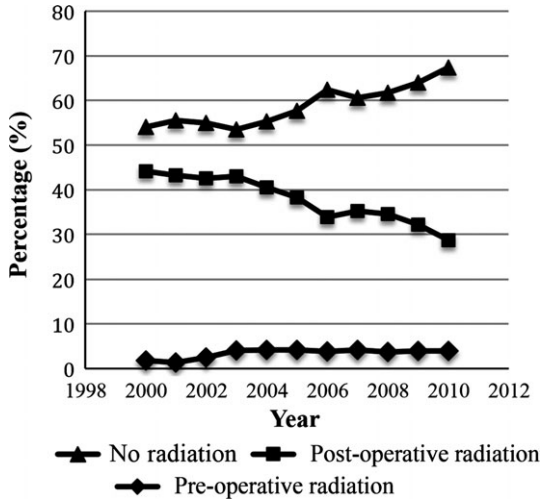


Figure 1 Trends in the use of radiation therapy for resectable pancreatic adenocarcinoma from 2000 to 2010

Survival analysis based on the type of treatment

In our unadjusted survival analysis models, the median survival for those who received pre-operative radiation was 23 months compared with 16 months for those who received no RT ($P \leq 0.05$). There was also a significantly improved median survival for those who received post-operative radiation therapy compared with those who received no RT (20 versus 16 months, $P \leq 0.05$) (Fig. 2). However, at 5 years the survival curves become indistinguishable.

On multivariate analysis, the use of either pre- or post-operative RT was associated with a significantly lower hazard of death compared with no RT [pre-operative RT hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.55–0.74; postoperative RT HR 0.69, 95% CI 0.65–0.73] (Table 3). A more recent year of diagnosis, female gender, and non-Hispanic white race were all associated with a decreased hazard of death (all $P \leq 0.05$). Patients aged 40–64 years had a significantly lower hazard of death compared with those aged 18–39 years (HR 0.41, 95% CI 0.32–0.53). Patients 65 years of age or greater also had a significantly lower hazard of death compared with those aged 18–39 years (HR 0.81, 95% CI 0.77–0.85). There was also significant geographic variation with regards to survival; however, no clear geographic trends emerged (Table 3). Tumour factors including larger tumour size, higher T-stage, higher tumour grade and lymph node positivity were all associated with an increased hazard of death (all $P \leq 0.05$).

Discussion

The data regarding the survival benefit of radiation therapy, when used in combination with chemotherapy, are inconsistent. Recommendations for the routine use of post-operative chemoradiation for the adjuvant treatment of pancreatic adenocarcinoma first came from the Gastrointestinal Tumor Study Group (GITSG) trial published in 1985, which showed a significant survival benefit for patients who received 5-fluorouracil and radiation in spite of a very small sample size owing to poor accrual.[1] A confirmatory study by GITSG confirmed this earlier study and concluded that the combined use of RT and fluorouracil as adjuvant therapy after a curative resection is preferred to no adjuvant therapy.[16] However, another randomized controlled trial, the European Organisation for Research and Treatment of Cancer (EORTC) trial 40891, showed no

Table 2 Predictors of receipt of pre-operative radiation therapy

Predictor	OR (95% CI)
Diagnosis year group	
2000–2004	*1.00 Referent*
2005–2010	**1.78 (1.360–2.331)**
Age categories	
18–39	0.38 (0.090–1.567)
40–64	**1.86 (1.453–2.384)**
65+	*1.00 Referent*
Gender	
Male	*1.00 Referent*
Female	0.92 (0.720–1.169)
Race	
Non-Hispanic white	*1.00 Referent*
Black	0.97 (0.661–1.411)
Other	1.11 (0.597–2.051)
Tumour size	
<2 cm	*1.00 Referent*
≥2 cm	**1.61 (1.011–2.573)**
Missing	1.47 (0.749–2.913)
Tumour grade	
1 or 2	*1.00 Referent*
3	1.001 (0.750–1.336)
4	1.05 (0.323–3.404)
Missing/unknown	**2.62 (1.892–3.622)**
T-stage	
1 and 2	*1.00 Referent*
3	**1.817 (1.305–2.531)**
4	**8.60 (5.629–13.142)**
Surgery type	
Whipple	*1.00 Referent*
Total pancreatectomy	1.02 (0.706–1.462)
Other	**0.55 (0.377–0.799)**
Node positive	
Yes	*1.00 Referent*
No	**0.348 (0.27–0.46)**
Nodes examined	
0	*1.00 Referent*
1–9	1.06 (0.649–1.748)
10–14	1.17 (0.689–1.975)
15+	0.75 (0.436–1.286)
Unknown	0.83 (0.336–2.063)
Registry	
Greater California	*1.00 Referent*
Utah	**4.06 (2.234–7.370)**
Metropolitan Detroit	**3.82 (2.474–5.893)**
Louisiana	**2.33 (1.397–3.899)**
Iowa	**2.20 (1.244–3.873)**
Connecticut	**2.11 (1.226–3.631)**
Metropolitan Atlanta	1.46 (0.717–2.963)
Greater Georgia	1.30 (0.745–2.269)
New Jersey	1.28 (0.822–1.993)
Seattle (Puget Sound)	1.07 (0.541–2.125)
Kentucky	0.98 (0.517–1.844)
Los Angeles	0.77 (0.425–1.382)

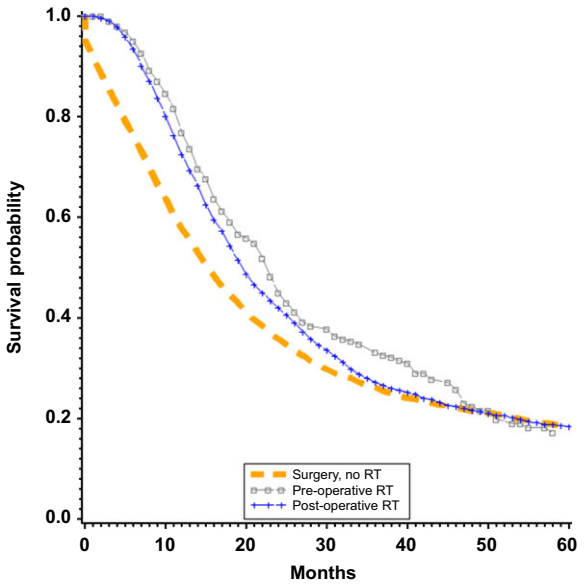
Cox's proportional hazard predictors of receiving pre-operative radiation therapy. Statistically significant predictors of pre-operative radiation therapy are in bold.
OR, odds ratio; CI, confidence interval.

significant survival benefit for patients treated with chemoradiation versus no chemoradiation. On further subgroup analysis, the EORTC 40891 trial demonstrated only a trend towards a significant improvement in survival in those patients with tumours in the head of the pancreas.[7] It is worth noting, however, that approximately 20% of patients assigned to chemo-radiotherapy did not receive the assigned treatment.

A population-based study using SEER published in 2008 demonstrated a survival benefit for the use of post-operative radiation therapy.[4] Our study confirmed the survival benefit associated with post-operative RT in the SEER registry. Two large single institutional studies also reported a survival benefit for those patients who received adjuvant chemoradiation versus no chemoradiation therapy.[2,3] However, the study by Corsini *et al.*[3] showed the survival benefit for chemoradiation was no longer significant for patients with both negative lymph nodes and low-grade tumours.

Another randomized controlled trial, the Radiation Therapy Oncology Group (RTOG) 9704 study, evaluated the survival benefit of gemcitabine versus fluorouracil before and after chemoradiation. This study found that the addition of gemcitabine was associated with a non-statistically significant improved survival rate but a marked increase in grade 4 hematologic toxicity.[5] A subsequent analysis performed by Abrams *et al.*[6] found that survival was significantly improved for those patients who received appropriate radiation as outlined by the trial protocol compared with patients who received radiation that did not meet the protocol guidelines; these findings suggest that appropriately administered post-operative RT may positively impact survival.

The results of the ESPAC-1 trial, first published in 2001, suggested that post-operative chemoradiation may have a deleterious effect on survival.[8] This study has been critiqued for a number of reasons including adherence to protocols on delivery of the RT and the crossover rates between treatment arms. However, its publication questioned the benefits of post-opera-



Number at risk by treatment type	0 months	30 months	5 years (60 months)
Surgery, No RT	5039	1973	1665
Pre-operative RT	299	145	113
Post-operative RT	3136	1304	998

Figure 2 Kaplan–Meier curves for overall survival based on the three treatment groups: surgery without radiation therapy (RT), pre-operative RT then surgery and surgery followed by post-operative RT

tive chemoradiation and may have influenced the treatment patterns for pancreatic adenocarcinoma in the United States. In a previous study using SEER, Shinohara *et al.* evaluated the use of post-operative RT 5 years before and 5 years after the initial publication of the ESPAC-1 trial in 2001[17,18] and found that the use of post-operative RT significantly decreased between 2001 and 2007. We demonstrate that the use of post-operative RT continued its decline first observed in 2001 through at least 2010.

While questions about the survival benefit of post-operative RT remain, a strategy of pre-operative adjuvant therapy offers a number of potential benefits for patients with adenocarcinoma of the pancreas.[10–14] First, a large proportion of patients do not receive recommended adjuvant therapy after surgery secondary to surgical complications.[2,3,7] A strategy utilizing pre-operative adjuvant therapy assures multimodality treatment to a higher proportion of patients and may improve survival. Second, delivering pre-operative therapy allows time for subclinical metastatic disease to become apparent, thus sparing patients an unnecessary operation if radiographic metastases are identified before surgery.[19] Third, pre-operative therapy has been associated with a lower likelihood of positive surgical margins and a lower risk of lymph node metastases.[20]

The present study found a significant survival benefit for both pre- and post-operative RT when compared with those patients receiving surgery alone. This is consistent with two previous SEER studies that also showed survival benefits for the use of RT when used in both the pre- and post-operative setting.[4,14] However, conflicting evidence about the survival benefits of post-operative RT remain and studies evaluating the survival benefits of pre-operative RT are largely observational. In addition, the results of randomized trials comparing pre- versus post-operative adjuvant therapy have not yet been published. However, in a recently published single-centre study of patients 70 years of age or greater, Cooper *et al.* reported that among patients treated with curative intent, the median overall survival of all patients who received chemoradiation therapy first (regardless of whether they underwent surgery) was similar to that of patients who underwent a resection first. On further analysis, this study did show that the median survival of patients who received pre-operative chemoradiation followed by surgery was 33.8 months as compared with 15.1 months for those treated with surgery first ($P = 0.001$).[21] This study is part of the growing literature that supports the use of a strategy that includes pre-operative adjuvant therapy.

In our study, we found a modest but significant increase in the use of pre-operative radiation therapy. To our knowledge, it is the first study to evaluate trends over time in the use of pre-operative radiation therapy. The use of pre-operative RT remains low (3.9%) overall, in spite of the statistically significant increase in use over the last 10 years. Our findings are similar to those reported by Colbert *et al.* who found that only 5% of their cohort of patients in the National Cancer Database (NCDB) received pre-operative radiation therapy.[20] These findings suggest that the overall use of pre-operative RT may be

Table 3 Cox proportional hazard model: 5-year relative hazard of death

	Hazard ratio	95% CI	*P* value
Treatment group			
No RT		*1.00 Referent*	
Pre-operative RT	**0.64**	**0.55–0.74**	**<0.0001**
Post-operative RT	**0.69**	**0.65–0.73**	**<0.0001**
Year			
2000–2004		*1.00 Referent*	
2005–2010	**0.85**	**0.81–0.90**	**<0.0001**
Age			
18–39		*1.00 Referent*	
40–64	**0.41**	**0.32–0.53**	**<0.0001**
65+	**0.81**	**0.77–0.85**	**<0.0001**
Gender			
Male		*1.00 Referent*	
Female	**0.90**	**0.86–0.95**	**0.0001**
Race			
Non-Hispanic white		*1.00 Referent*	
Black	**1.14**	**1.05–1.25**	**0.002**
Other or unknown	0.96	0.84–1.09	0.521
Tumour size			
<2 cm		*1.00 Referent*	
≥2 cm	**1.39**	**1.27–1.52**	**<0.0001**
Missing	**1.37**	**1.19–1.59**	**<0.0001**
Tumour grade			
1 or 2		*1.00 Referent*	
3	**1.39**	**1.31–1.47**	**<0.0001**
4	**1.78**	**1.42–2.23**	**<0.0001**
Missing/unknown	**0.83**	**0.75–0.93**	**0.0009**
T-stage			
1 and 2		*1.00 Referent*	
3	**1.39**	**1.30–1.49**	**<0.0001**
4	**2.03**	**1.79–2.30**	**<0.0001**
Surgery type			
Whipple		*1.00 Referent*	
Total pancreatectomy	**1.12**	**1.03–1.22**	**0.007**
Other	0.95	0.89–1.03	0.240
Node positive			
No		*1.00 Referent*	
Yes	**1.57**	**1.48–1.66**	**<0.0001**
Nodes examined			
1–14		1.00 Referent	
15+	**0.84**	**0.80–0.89**	**<0.0001**
Registry			
Connecticut		*1.00 Referent*	
Kentucky	**1.33**	**1.19 1.49**	**<0.0001**
Greater Georgia	**1.22**	**1.09 1.36**	**0.0002**
Louisiana	**1.18**	**1.05 1.33**	**0.006**
Iowa	**1.15**	**1.03 1.29**	**0.013**
Los Angeles	1.09	0.94 1.26	0.271
Metropolitan Atlanta	1.04	0.89 1.23	0.610
New Jersey	0.98	0.90 1.07	0.801
Seattle (Puget Sound)	0.93	0.80 1.07	0.271
Greater California	**0.88**	**0.80 0.97**	**0.009**
Utah	**0.86**	**0.75 0.97**	**0.021**
Metropolitan Detroit	**0.82**	**0.72 0.93**	**0.002**

Association between pre-operative radiation therapy (RT) and 5-year relative hazard of death. Statistically significant predictors of relative hazard of death are in bold

underutilized given the potential benefits of pre-operative adjuvant therapy that were discussed previously. Furthermore, we have shown in our study that the survival benefits for patients who received pre-operative RT are similar to those who received post-operative therapy, but improved as compared with those who received surgery alone. When taking these factors into account, one might expect a greater utilization of pre-operative adjuvant therapies including radiation therapy. However, the rates of pre-operative radiation therapy, while significantly increasing over this study period, still remain low.

Additionally, our study evaluated other factors associated with survival. Consistent with other population-based studies, we found that an increased risk of death was associated with larger tumour size, higher tumour grade and lymph node positivity.[4,20] Of note, a more recent year of diagnosis was associated with a decreased hazard of death. This finding is in contrast to a recently published large single-institutional study by Winter *et al.*[22] that demonstrated no improvement in long-term survival based on a decade of diagnosis. In fact, they note that the long-term survival of those patients who survived 1 year after surgery was significantly worse in the 2000s as compared to the 1990s.

Finally, this study also evaluated factors that influence the use of pre-operative radiation therapy. On multivariate analysis comparing those patients that received pre-operative RT with patients that received either surgery alone or surgery plus post-operative radiation therapy, we found that pre-operative RT was significantly associated with younger age, recent year of treatment, advanced T stage and type of surgical treatment. In the NCDB study, a univariate analysis was used to compare the group that received pre-operative RT with the group that received post-operative radiation therapy; this analysis found that lower T stage, higher use of chemotherapy and treatment

at an academic/research facility were significantly associated with pre-operative radiation therapy.[20] The association between pre-operative RT use and advanced T-stage in our study may be related to the increased use of pre-operative RT to potentially downstage larger and borderline-resectable tumours.

Our study has several SEER-related limitations. First, we cannot assess the role of misdiagnosis or whether the patient was diagnosed based on symptoms or on routine screening or imaging. Detailed patient and tumour information that may have influenced treatment decisions were not available from the cancer registry database. For example, we were unable to adjust for co-morbidities because these data are not collected by SEER. In addition, the impact, of treating facility volume and/or teaching status, could not be assessed with this data set. We were also unable to determine certain factors that may have influenced the use of adjuvant RT from the SEER database. For example, the presence of positive margins and the occurrence of post-operative complications may have impacted treatment decisions but were unable to be assessed. Also, we were unable to assess the impact of chemotherapy use because SEER does not collect these data. However, a number of other studies have shown that when RT is used, chemotherapy is almost uniformly used for the treatment of pancreatic adenocarcinoma.[3,20] Thus, while the data on chemotherapy use are not known for this cohort, the vast majority of those receiving RT were likely receiving chemotherapy as well. Another limitation of this study is the relatively small sample size of the pre-operative RT group (n = 299) compared with the post-operative RT and no RT groups. In addition, the overall quality of radiotherapy administered cannot be analysed. In spite of these limitations, the findings of our study provide important information about the use of pre-operative RT in the United States.

In conclusion, we found that administration of pre-operative RT significantly increased during the study period, but use remains low overall. We also noted significant variability in the use of pre-operative RT based on geographic regions. Thus, the overall use of pre-operative RT is likely underutilized, given the potential benefits of a pre-operative treatment strategy. However, this local variability offers a natural experiment to better understand the impact of the RT strategy on survival after pancreatic cancer diagnosis. Given the poor overall survival for persons diagnosed with pancreatic adenocarcinoma and the persistent questions on the timing and benefit of adjuvant therapy, further prospective randomized controlled trials are needed; we recommend randomized controlled trials specifically comparing pre- versus post-operative adjuvant therapies including radiation, chemotherapy and combined chemoradiation.

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Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

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